Remarks

In the Specification

The paragraph beginning on page 1, line 4 has been amended in order to update the status of Application Serial No. 09/645,786 (now U.S. Patent No. 6,669,718 B1) and to add the section heading "CROSS-REFERENCE TO RELATED APPLICATIONS." No new matter has been added.

In the Claims

Claims 9, 14, 16, 24, 29, 33 and 34 are amended herein to correct certain grammatical errors and, with respect to claims 1, 8, 15-16, 23, 30, 32 and 33 to recite "wherein said heparin treatment affects the clotting time of a blood sample from said patient." Support for these changes can be found in the claims as originally filed as well as in the Specification. Accordingly, no new matter has been added.

Rejections Pursuant to 35 U.S.C. §102(b)

Initially, in the Office Action, claim 30 was rejected under 35 U.S.C. §102(b) as being anticipated by CA 1 250 213. In support of that rejection, the Examiner asserted that "[s]ince CA 1,250,213 teaches the same weight ratio of sulfatide to phosphatide as recited in instant claim 30, the reagent taught by CA 1,250,213 would inherently perform the same function of determining heparin treatment effectiveness, especially when a patient's heparin level is 0 U/ml, which is a possible heparin level recited in claim 30. The situation when a patient's heparin level is 0 U/ml is equivalent to the APTT clotting test taught by CA 1,250,213 on blood samples not having heparin therein."

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Moreover, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the

inherency of that result or characteristic. MPEP 2112 (citing *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)). "In relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP 2112 (citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)).

Claim 30 has been amended herein to recite "said reagent can determine heparin treatment effectiveness in patients receiving sufficient heparin to have blood heparin levels between about 0 U/mL and about 6 U/mL, and said heparin treatment affects the clotting time of a blood sample from said patient." Support for this amendment appears on pages 5-6 of the specification, and in Figs. 2-3. Drawings alone may provide a "written description" of an invention as required by §112. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565, 19 USPQ2d 1111, 1118 (Fed. Cir. 1991). Accordingly, no new matter as has been added. The fact that CA 1 250 213 teaches a procedure for the photometric determination of activated partial thromboplastin time (APTT) and a reagent suitable for this purpose is insufficient in meeting the Examiner's burden of providing rationale or evidence tending to show inherency. MPEP 2112. There is no teaching or suggestion in CA 1 250 213 of relating clotting times to heprin treatment effectiveness, or suitable reagents for performing such an assay. More particularly, CA 1 250 213 does not teach or suggest a reagent which can determine heparin treatment effectiveness in patients receiving sufficient heparin to have blood heparin levels between about 0 U/mL and about 6 U/mL, and that the heparin treatment affects the clotting time of a blood sample from the patient. CA 1 250 213 does not teach or suggest each and every element as set forth in claim 30. Accordingly, in light of the present amendment, applicant respectively requests that the rejection be withdrawn.

Also in the Office Action, claim 16 was rejected under 35 U.S.C. §102(b) as being anticipated by Bader et al. In support of that rejection, the Examiner asserted that

the reagent taught by Bader et al. can inherently be used to determine the effectiveness of heparin therapy in a patient by measuring clotting time since the reagent taught by Bader et al. is for the determination of prothrombin clotting time in blood samples and claim 16 does not recite a concentration of heparin in the patient's blood, thus allowing the possibility that no heparin is present in the patient's blood, which is equivalent to the determination of clotting time in regular blood samples containing no heparin, as taught by Bader et al.

As noted above, a claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. Claim 16 is amended herein and recites, *inter alia*, "[a] reagent for the determination of the effectiveness of heparin treatment in a patient receiving same . . . wherein said heparin treatment affects the clotting time of a blood sample from said patient, and when a sufficient quantity of said reagent is contacted with **[[a]]** said blood sample from **[[a]]** said patient, said clotting time can be used to determine **[[to]]** the effectiveness of said heparin therapy to **[[the]]** said patient." Bader et al. cannot anticipate the present invention as they do not teach or suggest the relationship between clotting times and heparin treatment effectiveness, or suitable reagents and cartridges for performing such an assay. Accordingly, in view of the present amendment, applicant respectfully requests that the rejection be withdrawn.

Also in the Office Action, claims 1 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by Gailani et al. In support of the instant rejection, the Examiner asserted that the reagent taught by Gailani et al. can inherently be used to determine the effectiveness of heparin therapy in a patient by measuring clotting time, since the reagent taught by Gailani et al. is for the determination of clotting time in blood samples, and claim 1 recites that the heparin concentration in the patient's blood can be "up to 6 U/mL" which could be interpreted to mean a concentration of 0 U/mL, while claim 16 does not recite a concentration of heparin in the patient's blood, thus allowing the possibility that no heparin is present in the patient's blood. Both situations included

within the scope of claims 1 and 16 are equivalent to the determination of clotting time in regular blood samples containing no heparin, as taught by Gailani et al.

Claim 1 is amended herein and recites a reagent for the determination of the clotting time of a blood sample from a patient receiving heparin treatment . . . wherein said heparin treatment affects the clotting time of a blood sample from said patient. Also, claim 16 is amended herein and recites "said heparin treatment affects the clotting time of a blood sample from said patient" (receiving heparin treatment). There is no teaching or suggestion in Gailani et al. relating clotting times to heparin treatment effectiveness, or suitable reagents and cartridges for performing such an assay. The cited reference cannot be relied upon in support of the instant rejection. Accordingly, applicant respectfully requests that the rejection be withdrawn.

Also in the Office Action (Section 5), claims 16 and 33-34 are rejected under 35 U.S.C. §102(b) as being anticipated by Griffin et al. (WO 96/15457). In support of the rejection, the Examiner asserted that Griffin et al. use a procoagulant reagent to test plasma samples containing heparin in a final concentration of 0.5 U/ml and, therefore, Griffin et al. teach of a method and reagent for determining the clotting time in blood samples containing heparin in a low dose by combining the blood sample with a reagent containing tissue factor and a phosphatide. The Examiner further asserted that Griffin et al. also inherently teach of a reagent comprising tissue factor and a cofactor, wherein when an effective amount of the reagent is contacted with a blood sample having a heparin level between 0 and 6 U/ml, a predetermined degree of clotting is reached in less than 300 seconds, since the reagent taught by Griffin et al. (i.e., a tissue factor and a phosphatide) is the same as in the instant invention which performs this function, and the blood sample in Griffin et al. whose clotting time is measured contains a heparin level of 0.5 U/ml, which is included in the scope of instant claim 16 that does not recite a specific concentration of heparin in the patient's blood, and in the scope of instant claims 33-34 that recite a heparin concentration in the patient's blood between 0 and 6 U/ml.

Griffin et al., in WO 96/15457, teach at page 18 that up to 0.5 U/mL heparin in blood plasma did not alter the interpretation of test results from their thrombotic disorders assay, despite a "plasma concentration of exogenous heparin, which exceeds the plasma level recommended for continuous intravenous therapy with heparin." As noted herein, claim 16 has been amended to recite "[a] reagent for determination of the effectiveness of heparin treatment in a patient receiving same . . . wherein said heparin treatment affects the clotting time of a blood sample from said patient." Also, claim 33 has been amended herein to recite "said heparin treatment affects the clotting time of a blood sample from said patient." In light of the present amendment, Griffin et al. cannot be relied upon in support of the present rejection, as they do not teach or suggest each and every element as set forth in the claims. Moreover, Griffin et al. teach away from a reagent for the determination of the effectiveness of heparin treatment in a patient receiving same, that reagent comprising tissue factor and at least one co-factor selected from the group consisting of a phosphatide and a sulfatide, as heparin is viewed merely as a potential interferent, which had no impact on test result interpretation even when higher doses of heparin were present. In contrast, the present invention is directed to a reagent for the determination of the effectiveness of heparin treatment over a broad range of heparin doses. In light of the foregoing, applicant respectfully requests that the rejection be withdrawn.

Also in the Office Action (Section 6), claim 30 was rejected under 35 U.S.C. §102(b) as being anticipated by McDonald et al. (U.S. Patent No. 5,039,617). In support of the rejection, the Examiner asserted that since McDonald et al. teach the same weight ratio of sulfatide to phosphatide as recited in instant claim 30, the reagent taught by McDonald et al. would inherently perform the same function of determining heparin treatment effectiveness in patients having blood heparin levels between 0-6 U/mL, since McDonald et al. teach of the use of the reagent for the determination of clotting time in blood samples containing some level of heparin therein which is greater than 0, i.e., a heparin level of 0.1 U/mL or 0.3 U/mL.

As noted herein, a claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. Moreover, in relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. MPEP 2112.

Claim 30 is amended herein and recites a reagent for use in determining the effectiveness of heparin treatment in patients receiving same, comprising a sulfatide and a phosphatide, wherein . . . said reagent can determine heparin treatment effectiveness in patients receiving sufficient heparin to have blood heparin levels between about 0 U/ml and about 6 U/ml, and said heparin treatment affects the clotting time of a blood sample from said patient. In contrast, McDonald et al. disclose methods and devices for carrying out activated partial thromboplastin time (APTT) analysis on whole blood to which no anticoagulant has been added (*see* Abstract). In the example cited in the Office Action (Example 3 – Investigation of Sensitivity of APTT Measurement to Heparin Concentration), in order to arrive at blood heparin levels within the range recited in claim 30 of the present application, blood was drawn from 20 normal donors and **subsequently aspirated** into syringes containing zero, low, and high quantities of heparin. Blood volumes drawn thus resulted in whole blood heparin concentrations of about 0.1 U/ml (low heparin) and 0.3 U/ml (high heparin). *See* col. 16, lines 50-55.

The McDonald et al. patent is directed to a different assay and does not teach or suggest a reagent that can determine heparin treatment effectiveness in patients receiving sufficient heparin to have blood heparin levels between about 0 U/ml and about 6 U/ml. Accordingly, the Examiner has not met her burden of providing rationale or evidence tending to show inherency. Moreover, McDonald et al. do not teach or suggest all of the limitations recited in claim 30. Because of the reasons set out above,

the '617 patent cannot be relied upon in support of the instant rejection. Applicant respectfully requests that the instant rejection be withdrawn.

Rejections Pursuant to 35 U.S.C. §103(a)

Also in the Office Action (Section 9), claims 2-7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Gailani et al. By the Examiner's own admission, Gailani et al. fail to teach of the concentration levels of the tissue factor and sulfatide in the clotting reagent, fail to teach of freeze-drying the reagent, and fail to teach of the addition of buffers and stabilizing agents to the reagent. However, in support of the instant rejection, it is asserted that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to vary the concentration levels of the tissue factor and sulfatide in the reagent taught by Gailani et al. to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed. The Examiner further concluded that it also would have been obvious to one of ordinary skill in the art to freeze-dry the reagent and add a buffer and stabilizing agents to the reagent taught by Gailani et al. in order to preserve the reagent for an extended shelf life.

The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP 2142. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP 2142 (citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)). For the following reasons, applicant submits that the Examiner has not met this burden and respectfully requests that the rejection be withdrawn.

To establish a *prima facie* case of obviousness, *inter alia*, all of the claimed limitations must be taught or suggested by the prior art. MPEP 2143.03 (citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). The Galiani et al. patent does not fulfill this requirement as it does not teach or suggest a reagent for the determination of the clotting time of a blood sample from a patient receiving heparin treatment . . . wherein the heparin treatment affects the clotting time of a blood sample from the patient. The rejected claims (2-7) contain all of the limitations of the base claim (1) from which they depend. Therefore, contrary to the Examiner's assertion, it would not have been a matter of routine experimentation to vary the concentration levels of tissue factor and sulfatide in the reagent taught by Gailani et al. to the levels recited in the instant claims. There is no teaching or suggestion in Gailani et al. relating clotting times to heparin treatment effectiveness, or suitable reagents and cartridges for performing such an assay. Accordingly, the cited reference cannot be relied upon in support of the rejection under 35 U.S.C. §103(a). Applicant respectfully requests that the rejection be withdrawn, as the Examiner has not presented a *prima facie* case of obviousness.

Also in the Office Action (Section 10), claims 17-22 are rejected under §103(a) as being unpatentable over Griffin et al. By the Examiner's own admission, Griffin et al. fail to teach of the concentration levels of the tissue factor and phosphatide in the procoagulant reagent, fail to teach of freeze-drying the reagent, and fail to teach of the addition of buffers and stabilizing agents to the reagent. However, in support of the instant rejection, it is asserted that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to vary the concentration levels of the tissue factor and phosphatide in the reagent taught by Griffin et al. to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed. The Examiner further concluded that it also would have been obvious to one of ordinary skill in the art to freeze-dry the reagent and add a buffer and stabilizing agents to the reagent taught by Griffin et al. in order to preserve the reagent for an extended shelf life.

As noted above, in order to establish a *prima facie* case of obviousness, *inter alia*, all of the claimed limitations must be taught or suggested by the prior art. The Griffin et al. patent does not fulfill this requirement as it does not teach or suggest a reagent for determination of the effectiveness of heparin treatment in a patient receiving same . . . wherein said heparin treatment affects the clotting time of a blood sample from said patient. Instead, Griffin et al. teach at page 18 that up to 0.5 U/mL heparin in blood plasma did not alter the interpretation of test results from their thrombotic disorders assay, despite a plasma concentration of exogenous heparin, which exceeds the plasma level recommended for continuous intravenous therapy with heparin. Griffin et al. clearly teach away from the present invention – heparin is viewed merely as an interferent, which had no impact on test result interpretation even when higher doses of heparin were present. In contrast, the present invention is directed to a reagent for the determination of the effectiveness of heparin treatment over a broad range of heparin doses. The rejected claims (17-22) contain all of the limitations of the base claim (16) from which they depend. Therefore, contrary to the Examiner's assertion, it wouldn't have been a matter of routine experimentation to vary the concentration levels of tissue factor and phosphatide in the reagent taught by Griffin et al. to the levels recited in the instant claims. Applicant submits that the Examiner has not presented a *prima facie* case of obviousness and, therefore, respectfully requests that the rejection be withdrawn as Griffin et al. do not teach or suggest all of the claimed limitations.

Also in the Office Action (Sections 11 and 12), claims 8-15, 23-29 and 31 are rejected under §103(a) as being unpatentable over McDonald et al. in view of Gailani et al., and claims 23-29 and 31-32 are rejected under §103(a) as being unpatentable over McDonald et al. in view of Griffin et al., respectively. By the Examiner's own admission, McDonald et al. fail to teach that the capillary flow device can contain therein a reagent comprising tissue factor and a sulfatide. However, in support of the rejection of claims 8-15, 23-29 and 31, it is asserted that based on the combination of McDonald et al. and Gailani et al., it would have been obvious to one of ordinary skill in the art at the time of

the instant invention to include in the capillary flow device taught by McDonald et al. the reagent taught by Gailani et al. containing a tissue factor and a sulfatide, since McDonald et al. disclose that the reagent in the capillary flow device must serve to activate the intrinsic coagulation pathway of blood, and Gailani et al. teach the combination of a tissue factor and a sulfatide serves to activate the intrinsic coagulation pathway of blood. The Examiner further concluded that it also would have been obvious to one of ordinary skill in the art to vary the concentration levels of the tissue factor and sulfatide in the reagent taught by Gailani et al. to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed.

Moreover, with respect to the rejection of claims 23-29 and 31-32, the Examiner admitted that McDonald et al. fail to teach that the capillary flow device can contain therein a reagent comprising tissue factor and either a phosphatide or a sulfatide. However, in support of the instant rejection, it is asserted that based upon the combination of McDonald et al. and Griffin et al., it would have been obvious to one of ordinary skill in the art at the time of the instant invention to include in the capillary flow device taught by McDonald et al. the reagent taught by Griffin et al. containing a tissue factor and a phosphatide, since McDonald et al. disclose that the reagent in the capillary flow device must serve to activate the intrinsic coagulation pathway of blood, and Griffin et al. teach that the combination of a tissue factor and a phosphatide serves to activate the intrinsic coagulation pathway of blood. The Examiner further asserted that it also would have been obvious to one of ordinary skill in the art to vary the concentration levels of the tissue factor and phosphatide in the reagent taught by Griffin et al. to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed.

In order to establish a *prima facie* case of obviousness, *inter alia*, all of the claimed limitations must be taught or suggested by the prior art. Claims 8, 15, 23 and 32 are directed to a test cartridge for the determination of the clotting time of a blood sample from a patient receiving heparin treatment, wherein the clotting time is used to determine the effectiveness of the treatment. These claims are amended herein to further recite "wherein said heparin treatment affects the clotting time of a blood sample from said patient." As noted herein, McDonald et al. disclose methods and devices for carrying out APTT analysis on whole blood and, in the examples illustrating McDonald et al.'s invention, blood was drawn from normal donors and subsequently aspirated into syringes containing heparin. The McDonald et al. patent is directed to a different device for carrying out a different assay. It does not teach or suggest a test cartridge wherein clotting time is used to determine the effectiveness of heparin treatment in a patient receiving heparin treatment, and wherein said heparin treatment affects the clotting time of a blood sample from said patient. For the reasons noted herein, the disclosures of Galani et al. and Griffin et al. do not fulfill the deficiencies of McDonald et al. Moreover, rejected claims 9-14, 24-29 and 31 contain all the limitations of the base claim from which they depend. Accordingly, applicant submits that in light of the present amendment and remarks made herein, the Examiner has not presented a *prima facie* case of obviousness and respectfully requests that the rejections be withdrawn.

Applicant notes that in Application Serial No. 09/645,786 (now U.S. Patent No. 6,668,718), which is the parent of the present application, the Examiner stated in her reasons for allowance that none of the prior art of record teaches or fairly suggests a method for determining the effectiveness of heparin treatment in a patient receiving doses of heparin up to about 6 U/mL by determining the clotting time of a blood sample from the patient, wherein the clotting time is altered by the heparin treatment, and wherein the blood sample is contacted with one of the recited reagents (part of Paper No. 13).

Applicant further notes the remaining prior art cited in the Office Action (Griffin et al., U.S. Patent No. 6,083,757 which corresponds to WO 96/15457; Hawkins et al.; Brown; Brucato et al.; and Lee et al.). As that additional art is not applied by the Examiner against the claims of this application, applicant is not providing any comments concerning the same at this time.

Conclusion

Applicant has filed a complete response to the outstanding Office Action and respectfully submit that, in view of the above amendments and remarks, the application is in condition for allowance. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response. Otherwise, early notification of allowable subject matter is respectfully solicited.

Respectfully submitted,

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